REMARKS

Applicant respectfully requests that the amendments of this Response be entered under 35 U.S.C. § 114 [Request for continued examination]. In order that the 35 submitted claims may be reviewed in a simpler format (e.g., typical for claims after an Examiner's Amendment), Applicant also submits, for the convenience of the Examiner, "CLAIMS 119–153 RENUMBERED AS CLAIMS 1–35 AND REORDERED" as APPENDIX 1.

Terminal Disclaimer

The Office Action (Final) mailed November 16, 2006, states a rejection of claims 119–121, 123–129, 131–134 and 136–139 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–3 of U.S. Patent No. 6,716,824. Applicant submits the attached terminal disclaimer (i.e., a completed form PTO/SB/26) in order to obviate this rejection.

Enablement

The Office Action (Final) further states a rejection of claims 119–139 under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement. Applicant respectfully traverses this rejection for pending claims 119–153 (each of which is either a new claim or a claim that is effectively amended through the amendment of independent claims 119, 124, 127, 132 and 136).

That is, Applicant respectfully maintains that the present application enables amended pending claims 119–153. Applicant respectfully submits a "DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI" as APPENDIX 2 in order further to support this position. This Declaration in particular includes references to some of the pertinent papers for supporting enablement that were published before the filing date of parent patent application serial no. 09/686,631, now U.S. Patent No. 6,716,824 (i.e., October 11, 2000).

Before discussing enablement from a simple legal perspective, Applicant believes that additional perspectives on enablement may also be helpful. As noted in the prosecution history of parent patent application serial no. 09/686,631, the claims are directed to methods commonly

referred to as "**suicide gene therapy**" methods. Accordingly, Applicant provides a brief summary of relevant aspects of this technology.

"Suicide gene therapy" was invented by Dr. Savio Woo of the Baylor College of Medicine (see e.g., U.S. Patent Nos. 6,217,860; 6,066,624; and 5,631,236). The Baylor College of Medicine remains a leading institution in this therapeutic approach to treating cancer. The therapy is based on the principle of transfecting a suicide gene into tumor cells. The product encoded by the suicide gene converts a pro-drug into a drug that is toxic to dividing cells by interfering with DNA synthesis. Although non-tumor cells may also be transfected to some degree, tumor specificity is based on the fact that the drug is toxic to dividing cells, and thus preferentially targets rapidly dividing tumor cells. Specificity can be further enhanced with the use of tumor specific promoters and vectors.

The efficacy of suicide gene therapy also benefits from the well-known "bystander effect." The bystander effect results from the transfer of agents, e.g., viral thymidine kinase proteins, into neighboring cells through gap junctions. The neighboring cells will be killed when they try to divide. The bystander effect is one of the features that makes suicide gene therapy quite attractive as a cancer treatment option (e.g., see paragraph [0112] of published pending application US20050059620, which notes that, although only 10% of the cells were transfected, 26% of the cells were killed as a result of the bystander effect).

The novel promoter of the invention is called the "RIP" promoter, and is based on a portion of the Rat Insulin Promoter. The RIP promoter is combined with a cytotoxic gene (such as a thymidine kinase (TK) gene) to make a suicide gene construct (such as the "RIP-TK" suicide gene construct). Because the RIP promoter is an insulin promoter, its targeting expression in insulin-expressing tumors of the pancreas is reasonable. Insulin-expressing tumors of the pancreas derive from the beta cells and are also called "insulinomas" (to indicate that they secrete insulin) or "endocrine" tumors. Experimental data confirms that the RIP promoter targets cytotoxic gene expression (e.g., TK expression) to insulinomas [e.g., see FIG. 2 of published pending application US20050059620, wherein a significant decrease in cell survival of mouse insulinoma derived NIT-1 cells is shown when RIP-TK-transfected NIT-1 cells receive

the pro-drug ganciclover (GCV) but not when NIT-1 cells transfected with a hollow vector receive the pro-drug GCV].

Most pancreatic tumors, however, do not express insulin, and are known as "ductal" tumors (e.g., see paragraph [0006] of published pending application US20050059620). Surprisingly, the RIP promoter also allows expression in these non-insulin expressing, pancreatic tumor cells. Thus, cells of the human pancreatic ductal adenocarcinoma cell lines, PANC-1 and CAPAN-1, are targeted and killed by the RIP-TK and pro-drug combination (e.g., see paragraphs [0138] and [0139] of published pending application US20050059620). Subsequent experiments show that the expression of a factor called PDX-1 allows the RIP promoter to target these tumor cells even though they to not express insulin (e.g., see paragraphs [0063] and [0140] of published pending application US20050059620).

Although the RIP promoter can be used to target insulin-secreting tumors, surprisingly this promoter could also be used to target non-insulin secreting tumor cells that are PDX-1 positive. PDX-1 positive tumors constitute the bulk of pancreatic tumors. On request, Applicant will provide additional information on critical roles of the PDX-1 transcription factor, as well as on the major discovery that the **RIP promoter is susceptible to activation by PDX-1**.

Without prejudice as to other means for nucleic acids delivery, but in view of points of discussion on liposomal delivery that were covered during the interview of Friday, May 4, 2007, Applicant respectfully reiterates that Applicant has provided *in vivo* data demonstrating that liposomal delivery (e.g., of the RIP-TK construct) is efficacious. Applicant also respectfully maintains, as noted in APPENDIX 2 and the "DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI," that, in addition to direct administration of nucleic acid at the site of a tumor cell, systemic administration of nucleic acid, whether via liposomal delivery or adenoviral delivery, is enabled.

Concerning liposomal delivery, for example, after paragraph [0057] of published pending application US20050059620 concludes that "a liposomal gene delivery system was shown to be effective in vivo in scid mice," paragraphs [0068] and [0069], paragraphs [0130] through [0133], and paragraphs [0170] through [0174] further describe liposomal gene delivery systems. After describing in paragraph [0068] the injection of PANC-1 cells into scid mice and the liposomal

delivery of a RIP-tk gene construct (as well as a control RIP-lacZ gene construct) to the mice, paragraph [0069] reports:

> [0069] At necropsy, all nine mice treated with the gene therapy/GCV had no visible pancreatic tumors and one of nine had microscopic tumors on the liver. All control groups had large tumors. These data confirm that human PANC-1 cells can be selectively killed using systemic delivery of RIP-tk/GCV gene therapy.

A key result reported for the experiment noted at paragraphs [0130] and [0133] is the effectiveness of liposomal delivery of a RIP-TK gene construct into mice (i.e., five of six mice treated with the RIP-TK gene construct plus GCV lived, while all other mice that received the NIT-1 insulinoma cells "underwent a rapid decline in blood glucose values and died within sixty days of tumor inoculation"; the one mouse that died after having been treated with the RIP-tk gene construct had a technical problem in the receiving the RIP-tk gene construct-- the construct was injected into the mouse's bladder).

Finally, the specification notes in paragraph [0173] of paragraphs [0170] through [174]:

> [0173] ". . . The in vivo delivery of RIP-tk in combination with GCV resulted in a significant decrease in tumor burden in mice; the combination killed all PANC-1 tumors in eight of nine mice ($p<0.05$ compared to all other groups, ANOVA). Mice that received PANC-1 cells and treated with RIP-LacZ (the vector control) and mice treated with only GCV developed large peri-pancreatic intraperitoneal tumors."

In view particularly of the high level of skill in the art and the enabling state of the prior art (see APPENDIX 2 and the "DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI), the pending application, as indicated by these excerpts, enables systemic administration of nucleic acid, whether via liposomal delivery or adenoviral delivery, as well as direct administration of nucleic acid at the site of a tumor cell.

In *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the Federal Circuit reversed the Examiner's determination that claims directed to methods for detecting hepatitis B surface antigens did not satisfy the enablement requirement. The opinion provided factors to be considered in assessing enablement (often referred to as *Wands* factors), and these may include the following (as noted at Section 2164.01 (a) of the *Manual of Patent Examining Procedure, Eighth Edition* --incorporating Revision Five of August 2006):

(A) the breadth of the claims;

(B) the nature of the invention;

(C) the state of the prior art;

(D) the level of one of ordinary skill;

(E) the level of predictability in the art;

(F) the amount of direction provided by the inventor;

(G) the existence of working examples; and

(H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In *In re Wands*, the Federal Circuit found, among other things, that "there was considerable direction and guidance" in the specification, and that there was "a high level of skill in the art at the time the application was filed." *In re Wands*, 858 F.2d 731, 740, 8 USPQ2d 1400, 1406.

For the pending application, Applicant first respectfully notes that, in particular with regard to factor (A), Applicant has narrowed the breadth of the claims by amending each independent claim to require that "the administration of the nucleic acid is either by direct administration at the site of the tumor cell or by systemic administration via liposomal or adenoviral delivery." With regard to factor (B), Applicant respectfully wishes to distinguish the nature of Applicant's invention from gene therapy claims of others, which may be directed either to integrative genetic transformation [i.e., Applicant's claimed methods do not require integrative genetic transformation] or to a cancer cure [i.e., a claimed method of Applicant can be palliative or substantively life extending, e.g., through the killing of a cancer cell (and not necessarily the killing of an entire tumor), without providing the method's subject with a cancer cure].

With regard to factors (C) and (D), Applicant also respectfully notes in particular that, as supported by the "DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI" of APPENDIX 2, the state of the prior art can be viewed as providing a considerable amount of enabling aspects to the claimed methods, and the skill level of one of ordinary skill in the art is high for the claimed methods. With regard to factor (E), and for Applicant's field of RIP promoter-mediated suicide gene therapy, Applicant respectfully is <u>not</u> as pessimistic as others may be in other fields of gene therapy about the level of predictability.

With regard to factors (F) and (G), Applicant's disclosure provides considerable direction through a number of examples, such that, when combined in particular with the enabling aspects of the state of the prior art, as well as with the high level of skill for one of ordinary skill in the art, Applicant respectfully maintains that the present application enables amended pending claims 119–153. In this view, when one considers factor (H), the quantity of experimentation needed to make or use the invention based on the content of the disclosure is not undue, but rather reasonable.

In closing this section of the Response, Applicant again expresses sincere thanks to Examiners Sgagias and Crouch for the telephonic interview of Friday, May 4, 2007. Applicant respectfully asks to be informed, particularly in view of Applicant's thorough claim amendments, of enabled allowable subject matter at the earliest point possible in the prosecution of the application (as the instructions that conclude Section 2164.04 of the *Manual of Patent Examining Procedure, Eighth Edition* --incorporating Revision Five of August 2006 – direct).

CONCLUSION

In view of the foregoing, Applicant has addressed all issues raised in the Office Action (Final) mailed November 16, 2006. Further in view of the foregoing, Applicant believes the pending application is in condition for allowance, and Applicant respectfully requests issuance of a Notice of Allowance. Applicant's undersigned representative earnestly requests a phone call at 713-226-1285 should an issue arise that may be addressed telephonically concerning this application.

Respectfully submitted,
LOCKE LIDDELL & SAPP LLP

Date: May 16, 2007

Mark J. Gatschet
Mark J. Gatschet, Ph.D.
Reg. No. 42,569

Locke Liddell & Sapp LLP
JP Morgan Chase Tower
600 Travis, Suite 3400
Houston, Texas 77002
Phone: (713) 226-1200
Fax: (713) 223-3717

APPENDIX 1

CLAIMS 119–153 RENUMBERED AS CLAIMS 1–35 AND REORDERED

1 ~~119~~. A method of killing a pancreatic tumor cell that does not express insulin in a subject, the method comprising:

a) administering to ~~a~~ the subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO:1 operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the pancreatic tumor cell that does not express insulin or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in ~~a~~ the pancreatic tumor cell that does not express insulin, and

b) administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the pancreatic tumor cell that does not express insulin.

2 ~~120~~. The method of claim 1 ~~119~~, where the cytotoxic gene is the thymidine kinase gene.

3 ~~121~~. The method of claim 1 ~~119~~, where the cytotoxic gene is the thymidine kinase gene and the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside.

4 ~~123~~. The method of claim 1 ~~119~~ ~~121~~, wherein the administration of the nucleic acid is by direct administration at the site of the pancreatic tumor cell.

5 ~~122~~. The method of claim 1 ~~119~~ ~~121~~, wherein the administration of the nucleic acid is systemic.

6 ~~143~~. The method of claim 5 ~~122~~, wherein the systemic administration is via liposomal delivery.

7 ~~144~~. The method of claim 5 ~~122~~, wherein the systemic administration is via adenoviral delivery.

8 ~~124~~. A method of treating a PDX-1 positive pancreatic tumor cell ~~cells~~ in a subject, the method comprising:

a) administering to ~~a~~ the subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO:1 operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the PDX-1 positive pancreatic tumor cell or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in ~~a~~ the PDX-1 positive pancreatic tumor cell, and

b) administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the PDX-1 positive pancreatic tumor cell.

9 ~~125~~. The method of claim 8 ~~124~~, where the cytotoxic gene is the thymidine kinase gene.

10 ~~126~~. The method of claim 8 ~~124~~, where the cytotoxic gene is the thymidine kinase gene and the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside.

11 ~~146~~. The method of claim 8 ~~124~~, wherein the administration of the nucleic acid is by direct administration at the site of the pancreatic tumor cell.

12 ~~145~~. The method of claim 8 ~~124~~, wherein the administration of the nucleic acid is systemic.

13 ~~147~~. The method of claim 12 ~~145~~, wherein the systemic administration is via liposomal delivery.

14 ~~148~~. The method of claim 12 ~~145~~, wherein the systemic administration is via adenoviral delivery.

15 ~~127~~. A method of killing a pancreatic tumor cell in a subject, the method comprising:

a) administering to ~~a~~ the subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO:1 operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the pancreatic tumor cell or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in ~~a~~ the pancreatic tumor cell, and

b) administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the pancreatic tumor cell.

16 ~~128~~. The method of claim 15 ~~127~~, where the cytotoxic gene is the thymidine kinase gene.

17 ~~129~~. The method of claim 15 ~~127~~, where the cytotoxic gene is the thymidine kinase gene and the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside.

18 ~~131~~. The method of claim 15 ~~127~~ ~~129~~, wherein the administration of the nucleic acid is by direct administration at the site of the pancreatic tumor cell.

19 ~~130~~. The method of claim 15 ~~127~~ ~~129~~, wherein the administration of the nucleic acid is systemic.

20 ~~149~~. The method of claim 19 ~~130~~, wherein the systemic administration is via liposomal delivery.

21 ~~150~~. The method of claim 19 ~~130~~, wherein the systemic administration is via adenoviral delivery.

22 ~~132~~. A method of killing a tumor cell expressing PDX-1 in a subject, the method comprising:

a) administering to ~~a~~ the subject with a tumor cell expressing PDX-1, a nucleic acid comprising an adenoviral vector with an insulin promoter having SEQ ID NO:1 operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the tumor cell expressing PDX-1 or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in the tumor cell expressing PDX-1, and

b) administering a pro-drug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the tumor cell expressing PDX-1.

23 ~~133~~. The method of claim 22 ~~132~~, where the cytotoxic gene is the thymidine kinase gene.

24 ~~134~~. The method of claim 22 ~~132~~, where the cytotoxic gene is the thymidine kinase gene and the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside.

25 ~~151~~. The method of claim 22 ~~132~~, wherein the administration of the nucleic acid is by direct administration at the site of the tumor cell expressing PDX-1.

26 ~~135~~. The method of claim 22 ~~132~~, wherein the administration of the nucleic acid is systemic.

27 ~~152~~. The method of claim 26 ~~135~~, wherein the systemic administration of the nucleic acid is via liposomal delivery.

28 ~~153~~. The method of claim 26 ~~135~~, wherein the systemic administration of the nucleic acid is via adenoviral delivery.

29 ~~136~~. A method of killing a tumor cell expressing PDX-1 in a subject, the method comprising:

a) administering to ~~a~~ the subject with a tumor cell expressing PDX-1 a nucleic acid comprising a vector with an insulin promoter, said insulin promoter comprising multiple copies of SEQ ID NO: 2 operatively coupled to multiple copies of SEQ ID NO: 3 or 4, said insulin promoter operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the tumor cell expressing PDX-1 or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in the tumor cell expressing PDX-1, and

b) administering a pro-drug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the tumor cell expressing PDX-1.

30 ~~137~~. The method of claim 29 ~~136~~, where the cytotoxic gene is the thymidine kinase gene.

31 ~~138~~. The method of claim 29 ~~136~~, where the cytotoxic gene is the thymidine kinase gene and the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside.

32 ~~140~~. The method of claim 29 ~~136~~, wherein the administration of the nucleic acid is by direct administration at the site of the tumor cell.

33 ~~139~~. The method of claim 29 ~~136~~, wherein the administration of the nucleic acid is systemic.

34 ~~141~~. The method of claim 33 ~~139~~, wherein the systemic administration is via liposomal delivery.

35 ~~142~~. The method of claim 33 ~~139~~, wherein the systemic administration is via adenoviral delivery.